Low Birthweight at Term and the Timing of Fetal Exposure to Maternal Smoking

ABSTRACT

Objectives. This study was undertaken to evaluate the risk of small-for-gestational-age birth for women who stop smoking or begin to smoke during pregnancy.

Methods. Women with term singleton pregnancies from a hospital-based cohort of 11 177 were classified as (1) nonsmokers; (2) smoked throughout pregnancy; (3) smoked during first trimester only; (4) smoked during first and second trimesters only; and (5) smoked during second and third trimesters or during third trimester only. Risk of small-for-gestational-age birth according to smoking category was estimated and adjusted for confounding factors by logistic regression.

Results. Women who stopped smoking by the third trimester were not at increased risk of small-for-gestational-age birth compared with nonsmokers. Women who began smoking during the second or third trimester had an elevated risk of small-for-gestational-age birth (odds ratio [OR] = 1.83; 95% confidence interval [CI] = 1.25, 2.67) similar to that for women who smoked throughout pregnancy (OR = 2.20; 95% CI = 1.90, 2.54). Risk of small-for-gestational-age birth increased with the number of cigarettes smoked during the third trimester.

Conclusions. It is during the third trimester that smoking retards fetal growth, presenting a compelling opportunity for smoking cessation interventions. Programs must emphasize the importance of not resuming smoking late in pregnancy. (*Am J Public Health.* 1994;84:1127–1131)

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Introduction

Women who stop smoking during pregnancy give birth to heavier infants than those who continue to smoke throughout pregnancy.[1–6] However, the few studies investigating the effect of the timing of smoking cessation have not yielded consistent results. Rush and Cassano,[2] as well as Hebel et al.,[5] found that stopping smoking during pregnancy at any time up through the eighth month nullified the negative effect of smoking on birthweight but that stopping in the ninth month did not. In contrast, MacArthur and Knox concluded that women needed to stop by 16 weeks to nullify the effect of smoking, and that stopping between 16 and 30 weeks only moderated the effect on birthweight.[3]

Additionally, most studies report their findings as birthweight differences between nonsmokers, persistent smokers, and quitters[2,3,5] without distinguishing whether those differences resulted from short gestation or impaired fetal growth. As low birthweight in infants of smokers results largely from impaired fetal growth, a more direct measure of effect is the proportion of infants born small for their gestational age.[7] Such infants are known to be at increased risk of fetal mortality as well as of neonatal morbidity and mortality[8–10] (although their risk is not as great as that of infants who are very premature).

How the timing of smoking cessation during pregnancy influences the occurrence of small-for-gestational-age births has important public health implications for the planning of smoking cessation interventions for women of childbearing age. Additionally, it is important to examine the effects for women who begin smoking during pregnancy. This study examines the effect of changes in smoking habits during pregnancy on the occurrence of term undersized births.

Methods

The Delivery Interview Program, conducted at the Boston Hospital for Women from August 1977 to March 1980, was designed to study the association between late pregnancy outcome and a wide variety of exposures. Data collected from interviews and medical record reviews included medical and obstetric history, course of the current pregnancy, and infant outcome, as well as demographic information. Women were also asked about their smoking habits, including the number of cigarettes smoked per day during each trimester of pregnancy. A total of 12 718 women were interviewed and had their medical records reviewed. Further details of the study methodology have been presented elsewhere.[11]

For this analysis, the cohort was limited to the 11 177 women who gave birth to term, liveborn infants of known sex and on whom complete smoking information was available. Only term

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This paper was accepted October 11, 1993.

Editor's Note. See related editorial by Shelov (p 1066) in this issue.

TABLE 1—Percentage Distribution of Demographic and Medical Characteristics among Term Small-for-Gestational-Age (SGA) and Appropriate-for-Gestational-Age (AGA) Infants

	Term SGA, % (n = 1188)	Term AGA, % (n = 9989)	P
Maternal race			
White	66	78	<.001
Black	21	12	
Other	13	10	
Insurance			
Welfare recipient	25	14	<.001
Self-pay	9	9	
Insured	66	77	
Maternal age, y			
<20	13	7	<.001
20–24	23	16	
≥25	64	77	
Marital status			
Single	19	11	<.001
Married	73	84	
Other	8	5	
Education			
<High school graduate	19	12	<.001
High school graduate	26	20	
>High school graduate	55	68	
Began prenatal care after first trimester	14	9	<.001
First pregnancy	57	50	<.001
≥Two alcoholic drinks/day, first trimester	14	14	NS
Any infant malformation	9	9	NS
Maternal height <5 ft	14	6	<.001
Maternal body mass index[a] <18	10	6	<.001
Maternal weight gain, lb			
<15	14	6	<.001
15–25	42	29	
>25	44	65	
Pre-eclampsia	5	3	<.001
Urinary tract infection during pregnancy	8	6	<.01
DES exposure	2	1	<.01
Smoking by trimester			
None	56	72	<.001
Throughout	37	20	
First only	4	5	
First and second only	1	1	
Second and third only	3	2	

[a]Weight in kilograms divided by (height in meters)^2
Note. NS = not significant; DES = diethylstilbestrol.

pregnancies (37 or more weeks gestation) were investigated so as to assess the specific effects of smoking on the occurrence of growth retardation rather than of low birthweight. There were not sufficient numbers of preterm infants who were growth retarded to examine the effect of smoking on intrauterine growth in that population. Term infants were categorized as being small for gestational age if their birthweight was less than the 10th percentile for their gestational age and sex using the criteria established by Williams et al.[12] For gestational age, the obstetrician's best estimate at the time of birth, which was available for all women, was used instead of last menstrual period, which was missing for 10% of subjects and was more often missing for women of low socioeconomic status. The two methods were in good agreement, differing by less than 2 weeks for 95% of births.

Women were categorized into one of five groups, according to their smoking habits:

1. Nonsmokers: women who never smoked and those who stopped smoking prior to pregnancy were combined, as both our analyses and the literature indicate no residual effect of smoking prior to pregnancy on infant birthweight[2]
2. Smoked throughout pregnancy
3. Smoked during the first trimester of pregnancy only
4. Smoked during the first and second trimesters of pregnancy only
5. Smoked during the second and third trimesters or during the third trimester only. These women began smoking during either the second trimester (n = 158) or the third trimester (n = 70) and continued to smoke for the remainder of pregnancy. These could represent women who stopped smoking prior to pregnancy and relapsed prior to delivery. Groups starting at different times were combined because of small numbers.

The crude risk of small-for-gestational-age birth according to smoking category was determined. Logistic regression analysis was used to determine the risk for each smoking category while controlling for the following potential confounding factors: maternal education, race, age, marital status, payment source, height, body mass index, pregnancy weight gain, parity, late prenatal care, and medical conditions (pre-eclampsia, urinary tract infection, and history of in utero diethylstilbestrol [DES] exposure). The logistic regression model contained four indicator variables for smoking status (a separate variable for each category of smokers), with nonsmokers as the referent group; the relative risk of small-for-gestational-age birth was determined for each smoking category relative to the nonsmoking group. In all logistic regression analyses, odds ratios (ORs) calculated from regression coefficients were used as estimates of relative risk. Confidence intervals (CIs) were calculated from the standard errors of those coefficients.

Risk of small-for-gestational-age birth could be influenced not only by changes in smoking habits but also by the number of cigarettes smoked. To investigate this, logistic regression was used to estimate the association of such a birth with smoking cessation independently for the two subgroups of smokers for whom there were adequate numbers: light smokers (up to 10 cigarettes per day; n = 1613)

and moderate smokers (11 to 20 cigarettes per day; n = 1098). Those women smoking more than 20 cigarettes per day (n = 428) and those who began smoking during pregnancy (n = 228) were not evaluated because of small numbers. Women were categorized according to first trimester smoking habits, as this was the only time when all the women being evaluated smoked.

In addition to evaluating the occurrence of small-for-gestational-age births, a dichotomous outcome, this study also used multiple linear regression (with birthweight as the dependent variable) to investigate the effect of changes in smoking habits on mean birthweight among term infants. In addition to the confounders noted above, gestational age and infant sex were included in these regression models, as infants of 40 weeks' gestational age are somewhat heavier than 37-week infants and male infants are heavier than female infants. Predicted differences in birthweight and the 95% confidence intervals relative to the nonsmoking group were calculated.

Results

There were 11 177 women with term singleton births included in the current analysis. Within the study population, 1188 (10.6%) women gave birth to small-for-gestational-age infants. Women giving birth to such infants differed in various ways from women whose infants were of appropriate size (Table 1). They were more likely to be Black, on welfare, single, less educated, less than 20 years of age, and primiparous; to begin prenatal care later in pregnancy; and to have medical conditions. Additionally, mothers of undersized infants tended to be shorter and thinner (low body mass index), and to gain less weight during pregnancy. These potential confounders were entered into the multivariate model.

Thirty percent (n = 3367) of the women in this cohort smoked at some time during pregnancy (Table 2). Of the smokers, 2449 (73%) smoked throughout pregnancy, 690 (20%) smoked early in pregnancy but quit, and 228 (7%) did not smoke during the first trimester but began to smoke during the second or third trimester and continued through the end of pregnancy. The frequency of small-for-gestational-age births differed according to smoking category (Table 2). Women who smoked throughout pregnancy were at about twice the risk of giving birth to undersized infants than were nonsmokers (17.7% vs 8.5%). For women who smoked only during the first trimester or during the first and second trimesters and then stopped, the risk was similar to that for nonsmokers (8.7% and 7.2%, respectively, vs 8.5%), while women who began smoking during the second or third trimester of their pregnancy had a rate of small-for-gestational-age birth close to that for women who smoked throughout pregnancy (15.4% vs 17.7%).

These associations did not change in logistic regression analyses that controlled for the potential confounding factors described earlier. The risk of giving birth to an undersized infant for women who smoked during either the first trimester only (OR = 1.04; 95% CI = 0.76, 1.43) or the first and second trimesters (OR = 0.83; 95% CI = 0.43, 1.61) was similar to that for nonsmokers. Women who began smoking during the second or third trimester were at increased risk of such an outcome (OR = 1.83; 95% CI = 1.25, 2.67), as were those who smoked throughout pregnancy (OR = 2.20; 95% CI = 1.90, 2.54). As maternal weight gain could mediate the effect of smoking on fetal growth, an additional analysis was performed without this factor; our results were virtually unchanged.

Women who smoked throughout pregnancy also smoked, on average, more cigarettes per day than those who stopped smoking (Table 2). To disentangle the effects of duration from the effects of quantity, logistic regression analyses were performed (controlling for confounders above) to determine the association of changes in smoking habits and risk of small-for-gestational-age birth separately for light and moderate smokers. Light smokers were those who smoked up to 10 cigarettes per day in the first trimester whereas moderate smokers were those

TABLE 2—Frequency at Term of Small-for-Gestational-Age Births, According to Smoking by Trimester

Smoking by Trimester	No. of Women	Frequency of Small-for-Gestational-Age Births, %	Mean No. of Cigarettes/day
Nonsmoker	7810	8.5	0
Smoked throughout	2449	17.7	15.3[a]
Smoked first trimester only	552	8.7	10.8[a]
Smoked first and second trimesters only	138	7.2	13.5[a]
Smoked second and third or third trimester only	228	15.4	7.7[b]
Total	11 177	10.6	

[a]For comparability, estimates for these groups are based on the number of cigarettes/day smoked during the first timester.
[b]Estimates are based on the number of cigarettes/day smoked during the third trimester, since women in this group did not smoke during the first timester.

TABLE 3—The Risk of Small-for-Gestational-Age Birth at Term for Light and Moderate Smokers, According to Maternal Smoking by Trimester[a]

	Light Smokers[b] (n = 1613)		Moderate Smokers[c] (n = 1098)	
Infant's Exposure to Smoking, by Trimester	Odd Ratio	95% Confidence Interval	Odd Ratio	95% Confidence Interval
All trimesters[d]	2.0	1.7, 2.4	2.4	2.0, 3.0
First trimester only	1.0	0.7, 1.5	1.1	0.6, 2.1
First and second trimesters only	0.6	0.2, 1.5	1.2	0.4, 3.6

[a]With nonsmokers (n = 7810) as referent group.
[b]≤ 10 cigarettes/day in first trimester.
[c]11–20 cigarettes/day in first trimester.
[d]Excluding women who smoked only in the third trimester.

TABLE 4—Adjusted Odds Ratio (AORs) and 95% Confidence Intervals (CIs) of Small-for-Gestational-Age (SGA) Birth at Term, According to Number of Cigarettes Smoked during the Third Trimester

Cigarettes/ Day	No. of Women	Percentage of SGA Births	AOR (95% CI)[a]
0	7810	8.5	1.0 (referent group)
1–5	685	14.7	1.69 (1.33, 2.14)
6–10	649	18.0	2.16 (1.72, 2.72)
>10	1343	18.7	2.48 (2.08, 2.95)

[a]From a multiple logistic regression model controlled for education, race, payment source (insured, welfare, other), age, marital status, body mass index, height, weight gain, late prenatal care, parity, exposure to diethylstilbestrol (DES), hypertension, urinary tract infection.

who smoked 11 to 20 cigarettes per day in the first trimester. For both groups, the effect of smoking throughout pregnancy and of smoking cessation were similar to that for the overall cohort. Light smokers had an odds ratio of 1.78 (95% CI = 1.44, 2.20) for the occurrence of undersized birth whereas the odds ratio for moderate smokers was 2.55 (95% CI = 2.10, 3.09). For both groups, women who stopped smoking did not have a significantly increased risk of small-for-gestational-age birth when compared with nonsmokers (Table 3). These data indicate that the effect observed in the overall cohort was not solely owing to the fact that women who stopped smoking were initially lighter smokers. Additionally, while women who started smoking during the second or third trimester smoked fewer cigarettes on average than women who smoked throughout pregnancy, their risk of small-for-gestational-age birth was nearly the same as that for continuous smokers.

To assess the association of changes in smoking habits during pregnancy with infant birthweight, a linear regression analysis was performed. The regression model included as independent variables smoking group and the potential confounding factors noted above, as well as infant sex and gestational age. The model predicted that infant birthweight for women who stopped smoking by the second or third trimester was essentially identical to that predicted for nonsmokers. (Linear regression predicted that infant birthweight for those women who smoked only in the first trimester was 0.8 g lighter than that for nonsmokers, whereas those women who smoked in the first and second trimester had a predicted infant birthweight that was 1.6 g lighter than that for nonsmokers.) Women who smoked throughout pregnancy had infants who were 186 g lighter than those of nonsmokers (95% CI = 170, 202 g) whereas the infants of those who started smoking during the second or third trimester were, on average, 138 g lighter than the infants of nonsmokers (95% CI = 82, 194 g).

Given that smoking seems to act during the third trimester to increase the risk of term undersized birth, the next step was to examine the influence of amount smoked during the third trimester. Third trimester smoking was categorized as none, 1 to 5 cigarettes per day, 6 to 10 cigarettes per day, or more than 10 cigarettes per day. The frequency of small-for-gestational-age births according to quantity smoked during the third trimester (Table 4) indicates an increased risk for heavier smokers (χ^2 for trend, $P < .0001$). A logistic regression analysis that included all the potential confounding factors described above indicates odds ratios for the risk of undersized birth that increase with the amount smoked during the third trimester (Table 4).

Discussion

Our analysis of growth retardation among term infants born to smokers indicates that the risk can be reduced to that for nonsmokers if smoking is stopped before the third trimester, while the risk for those who do not smoke early in pregnancy but smoke in the third trimester will be similar to that for continuous smokers. Results from our analysis concur with those of Rush and Cassano.[2] MacArthur and Knox, on the other hand, found a more limited benefit with regard to infant birthweight for women who stopped smoking between 16 and 30 weeks.[3] In that study, however, women who stopped smoking later in pregnancy (later than 16 weeks) were of lower socioeconomic status than women who stopped earlier. Therefore, failure to adjust for socioeconomic status could account for the lower birthweights noted by these authors among infants of women who stopped smoking later in pregnancy.

Our results, taken together with those of the other studies, suggest that the effect of cigarette smoking on growth retardation occurs during the third trimester of pregnancy. This is also consistent with previous work demonstrating that for babies born early in the third trimester (at 30 to 31 weeks), smoking was not associated with the occurrence of growth retardation.[13]

Finally, our investigation indicates that while any smoking during the third trimester is associated with an increase in undersized birth, the risk also increases with the amount smoked. Studies of smoking and birthweight have not consistently noted a dose response. Rush and Cassano found that infants of heavy smokers (more than 15 cigarettes per day throughout pregnancy) had a crude mean birthweight that was 163 g lighter than infants of women who smoked fewer than 5 cigarettes per day[2]; women smoking 5 to 14 cigarettes had infants with birthweights similar to those born to the highest smoking group. Butler and Goldstein, in investigating smoking after the fourth month of pregnancy, found similar results with women smoking fewer than 5 cigarettes per day giving birth to infants with a mean birthweight that was 120 g lighter than those born to smokers of 20 to 30 cigarettes per day, whereas smokers of 5 to 20 cigarettes had infants with intermediate birthweights.[1] Control for confounders did not alter these findings. Hebel et al. examined birthweight according to amount smoked at the eighth month while controlling for confounding factors.[5] In contrast to our findings and to those cited above, they found no dose response for birthweight according to amount smoked at 8 months of pregnancy.

The potential impact on the occurrence of small-for-gestational-age birth if women did stop smoking during the third trimester is substantial. In this population, 24% of women (n = 2677) smoked during the third trimester and their risk of small-for-gestational age birth was 17.5%. If all the smokers in this cohort had stopped smoking (and their rate of undersized births was that of nonsmokers), the rate of small-for-gestational-age infants in the population overall would have been reduced from 10.6% to 8.5%, a 20%

reduction. This is consistent with the findings of Kleinman and Madans,[14] who estimated that low birthweight would decrease by 19% if all women stopped smoking, and with the findings of Kramer,[15] who estimated that, for a population in which 20% of women smoke, the etiological fraction for cigarette smoking as a cause for intrauterine growth retardation was 22%.

While smoking cessation programs have met with limited success, the evidence that smoking acts during the third trimester to retard fetal growth presents a compelling opportunity for intervention at a time when many women may be motivated to alter their behavior. Such interventions need to emphasize the importance of not relapsing and smoking late in pregnancy. It is also important to emphasize to women that these results should not be interpreted to mean that it is safe to smoke during early pregnancy. Smoking during pregnancy has been associated with a number of adverse pregnancy outcomes other than growth retardation, including placenta previa,[16] premature rupture of membranes,[17] and preterm birth,[18] and it is not clear when during pregnancy smoking acts to increase the risk of these events. Additionally, smoking cessation would result in long-term health benefits for the woman and would decrease her child's exposure to environmental tobacco smoke. □

Acknowledgments

The Delivery Interview Program was supported by a grant from the March of Dimes Birth Defects Foundation.

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